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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,796	04/14/2004	Michael Kadan	3802-123-27	6667

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,796	KADAN ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *3 and 10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-9, and 14-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/07/05, 10/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Clams 1-26 are pending.

Election/Restrictions

1. Applicant's election with traverse of Group III, claims 5-17 and 19 in the scope of E2F and E1a in the reply filed on 12/15/2005 is acknowledged. The traversal is on the ground(s) that group V, claims 21-26 drawn to the method of producing the Hela S3 cell comprising the replication-competent adenovirus should be rejoined with elected group III since there is no extra burden for searching all of the limitations of claimed subject matter in group III. Upon reconsidering the pending claims, claims 1-2, 4-9 and 14-19 in the scope of E2F and E1a are rejoined and considered before the examiner. Regarding to the method claims from, the rejoin will not be considered until the time when the product claims 1-2, 4-9 and 14-19 in the condition for allowance as indicated in the previous office action.

2. Applicants are remind to amend the claims in the scope of E2F and E1a coding region for reflecting the scope that is under the examination on the merits.

3. The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 4 recites the limitation "tumor-specific replication-competent adenovirus vector" in claim 1. There is insufficient antecedent basis for this limitation in the claim 1 because claim 1 does not have the limitation of "tumor-specific replication-competent adenovirus vector"

6. Claims 14 and 15 are vague and indefinite in that they fail to define the structure of claimed vector comprised by the claimed Hela S3 cell. In particular, the claims do not define what the second gene is.

7. Claim 16 is vague and indefinite in that the claim fails to define where the heterologous gene is inserted into the claimed vector. This affects the dependent claim 17.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-2, 4-9, 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

10. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would render undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988) set forth below: 1). Nature of invention: 2). Scope of the claims; 3). Level of skill in the art, 4). State of art; 5). Unpredictability, 6). Number of working example; and 7). Amount of guidance presented in the specification.

11. The nature of the invention is directed to a Hela S3 cell line that can be used for propagating any or all adenovirus vector.

12. The state of art teaches that the entry of adenoviruses into susceptible cells requires two distinct sequential steps. The initial high affinity binding of Ad2 and Ad5 to the primary cellular receptors, identified as the coxsackievirus and adenovirus receptor (CAR) and the α2 domain of the major histocompatibility complex (MHC) class I protein[8], occurs via the C-terminal knob domain of the Ad fiber protein. Subsequent internalization of the virion by receptor-mediated endocytosis is potentiated by the interaction of Arg-Gly-Asp (RGD) peptide sequences in the penton base with secondary host cell receptors, integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. The virion then escapes from the endosome and localizes to the nuclear pore whereupon its genome is translocated to the nucleus (See Douglas et al. nature Biotechnology Vo. 17, pp. 470-475). However, not all adenovirus serotypes contain an RGD

sequence in their penton base subunits, therefor, the interaction with integrins may not be universal as evinced by Bai et al. (J. Virol. 1994, Vol. 68, No. 9, pp. 5925-5932, see page 5932, right column). Therefore, it is unpredictable that any or all adenovirus can utilize the Hela S3 cell for efficiently propagation.

13. The specification of current application only teaches that adenovirus vector made by serotype 5 and serotype 35 are able to efficiently infect and replicate in Hela S3 cell. The specification does not provide sufficient evidences to support the broadly claimed scope of invention that read on any or all replication-competent adenovirus vector is able to transducer and replicate Hela S3 cell. The specification does not provide adequate guidance to teach which serotype of adenovirus is able to infect and replicate well in such Hela S3 cell. There are so many serotypes of adenoviruses in the art.

14. Hence, considering large quantity of experimentation needed, the unpredictability of the field, the state of the art, and breadth of the claims, it is concluded that undue experimentation would be required to enable the intended claim.

15. Moreover, regarding to claim 4, it appears from reading the specification that for a successful viral rescue of replication-competent adenovirus having E1a deletion or mutation in claim 4. The sate of art also teaches that adenovirus vector lacking E1a and E2 can not propagate well in the host cell 293 that only contains the complement E1 function (See Zhou et al. J. Virol. 1996, Vol. 70, No. 10, pp. 7030-7038, see 7030). However, the specification does not provide a reproducible method to make such Hela S3 cell or any direction to obtain such Hela S3 cell clone. Hence, it would require an undue experimentation to enable the invention. Therefore, deposit of such Hela S3 cell line clone is required.

16. For the reasons discussed above, it is apparent that the Hela S3 cell specifically recited in the claim 4 is required to practice the claimed invention. As a required element they must be known and readily available to the public or obtainable by repeatable method set forth in the specification, or otherwise readily available to the public. If not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposits of said Hela S3 cell. See 37 CFR 1.802.

17. If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

18. If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

19. (a) during the pendency of this application, access to the deposits will be afforded to one determined by the commissioner to be entitled thereto; (b) all restrictions imposed by the depositor on the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application; (c) the deposits will be maintained in the public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; (d)a viability statement in accordance with the provisions of 37 CFR 1.807; and (e) the deposits will be replaced if they should become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

20. In addition, the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-37 CFR 1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 1-2 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Bai et al. (J. Virol. 1994, Vol. 68, No. 9, pp. 5925-5932) in view of the disclosures of Stanziale et al. Current Molecular Medicine Feb. 2003, Vol. 3, pp. 61-71, especially see pages 64-66) and Turturro et al (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640).

23. Claims 1 and 18 are directed to a Hela S3 cell or such cell line comprising a replication competent adenovirus vector, wherein said replication-competent adenoviruis vector is interpreted by the specification as adenoviral vectors and particles preferentially replicate in certain types of cells or tissues but to a lesser degree or not at all in other types. In one embodiment of the invention, the adenoviral vector and/or particle selectively replicates in tumor cells and or abnormally proliferating tissue, such as solid tumors and other neoplasm. Such viruses may be referred to as "oncolytic viruses" or "oncolytic vectors" and may be considered to be onco-cytolytic" or "cytopathic" and to effect (selective cytolysis" of target cells). (Please see lines 14-20 on page 10).

24. Bai et al. teach a Hela S3 cell comprising a wild-type adenovirus and support said virus replication (See pages 5927). The wild-type adenovirus is considered to be oncolytic regardless of it as a mutant viral vector or just a wild-type virus in view of the disclosure by Stanziale et al. Current Molecular Medicine Feb. 2003, Vol. 3, pp. 61-71, especially see pages 64-66), and adenovirus is more preferably or susceptibly in the cancel cell line of Hela S3 in view of the disclosure by Turturro et al. (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640). The adenovirus is characterized to support the tumor specific adenovirus infection and replication in view of the disclosure by Turturro et al (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640). Turturro et al. teach that Hela S3 cell expresses high level of coxsackie-adenovirus receptor (CAR) and $\alpha v\beta$ integrins that makes it more susceptible for adenovirus infection and more efficiently propagation compared with other cell type that express much less levels of these molecules. Therefore, the claims are anticipated by the cited reference.

25. Claims 1-2, 4 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al. (J. Biol. Chem. 1994, Vol. 269, No. 15, pp. 11542-11546) in view of the disclosures by Yoshimura et al (J. Bio. Chem. 1993, Vol. 268, No. 4, pp. 2300-2303), Stanziale et al. Current Molecular Medicine Feb. 2003, Vol. 3, pp. 61-71, especially see pages 64-66) and Turturro et al (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640).

26. Claims 1-2, 4 and 18 are directed to a Hela S3 cell or such cell line comprising a replication competent adenovirus vector, more preferably said adenovirus vector having E1a gene mutation or deletion (claim 4), wherein said replication-competent adenoviruis vector is interpreted by the specification as adenoviral vectors and particles preferentially replicate in certain types of cells or tissues but to a lesser degree or not at all in other types. In one embodiment of the invention, the adenoviral vector and/or particle selectively replicates in tumor cells and or abnormally proliferating tissue, such as solid tumors and other neoplasm. Such viruses may be referred to as "oncolytic viruses" or "oncolytic vectors" and may be considered to be onco-cytolytic" or "cytopathic" and to effect (selective cytolysis" of target cells). (Please see lines 14-20 on page 10).

27. Wu et al. teach a Hela S3 cell that is able to support the a wild-type adenovirus or a mutated adenovirus Ad-dl312 infection and replication (See pages 11543-11544), wherein the Ad-dl321 has E1a mutation in view of the disclosure by Yoshimura et al. see page 2300). The wild-type adenovirus is considered to be oncolytic regardless of it as a mutant viral vector or just a wild-type virus in view of the disclosure by Stanziale et al. Current Molecular Medicine Feb. 2003, Vol. 3, pp. 61-71, especially see pages 64-66), and adenovirus is more preferably or susceptibly for the cancel cell line of Hela S3 infection and replication in view of the disclosure by Turturro et al. (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640). Turturro et al. teach that Hela S3 cell and other cancer cell line express high level of coxsackie-adenovirus receptor (CAR) and $\alpha v\beta$ integrins that make them more efficiently for the adenovirus transducing and replication compared with other cell type that express much less levels of these molecules. Therefore, the claims are anticipated by the cited reference.

Claim Rejections - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. Claims 1-2, 5-9, 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/067861A2 and Turturro et al (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640).

30. The claimed invention is directed to a Hela S3 cell line comprising an adenovirus vector comprising an E2F promoter operably linked to the E1a gene and a therapeutic gene of GM-CSF.

31. WO 02/067861A2 discloses a recombinant adenovirus vector comprising an adenovirus serotype 5 or serotype 35 nucleic acids backbone, wherein said nucleic acid backbone comprises a left ITR, a terminal signal sequence, an E2Fresponsive promoter which is operably linked to E1a gene and an adenovirus packing signal and a right ITR. The recombinant viral vector further comprises a therapeutic gene, such as GM-CSF (See claims 1, 2, 3, 4, 5, 18, 21, 23). WO 02/067861A2 does not teach to use Hela S3 to propagate such recombinant adenovirus vector.

32. Turturro et al. teach that Hela S3 cell and other cancer cell line express high level of coxsackie-adenovirus receptor (CAR) and $\alpha v\beta$ integrins that make them more efficiently for the adenovirus transducing and replication compared with other cell type that express much less levels of these molecules.

33. Therefore, it would have been obvious for a person with ordinary skill in the art in order to propagate the adenovirus more efficiently to chose the Hela S3 cell as a host cell for more efficiently to propagate the adenovirus vector absence unexpected result since WO 02/067861 already teaches the adenovirus vector and Turturro et al. teach that the Hela S3 cell is a very good host cell that can be inefficiently transduced by an adenovirus vector. As there are no unexpected results have been provided, hence the claimed invention as a whole is prima facie obvious absence unexpected results.

Conclusion

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 7:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bao Qun Li

BAOQUN LI, MD
PATENT EXAMINER

102/16/2006